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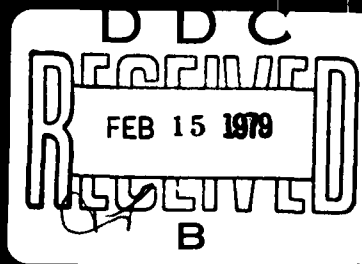
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PHARMACOKINETICS AND METABOLISM
OF CANDIDATE ANTIMALARIAL DRUGS

July 1975
Final Report

by

Charalingayya B. Hiremath, Ph.D.

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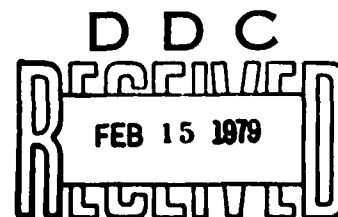
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Title of Report: Pharmacokinetics and Metabolism of Candidate
Antimalarial Drugs (WR-171,669-C¹⁴, WR-159,412-C¹⁴,
WR-33063-C¹⁴, WR-172,435-C¹⁴ and WR-184,806-C¹⁴)
In Experimental Animals.

Principal Investigator: Charalingayya B. Hiremath, Ph.D.

Contractor: Litton Bionetics, Inc.

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Submitted by:

Robert J. Veir (for)

Robert J. Veir, Ph.D.
Vice-President, Biological Safety and Evaluation Division

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ABSORPTION, DISTRIBUTION AND EXCRETION OF WR-171,669-¹⁴C IN THE RAT

Radiochemically pure WR-171,669-¹⁴C was orally administered to male Sprague-Dawley rats at a dose of 20 mg/kg. Initial studies (Report I, Jan. 26, 1973) with three animals provided evidence that the compound at 0-6 hr, 6-24 hr and 24-48 hr was: 1) absorbed by the gut, 2) distributed broadly in the tissues (43% of dose in carcass at 24 hr), and 3) excreted principally in the feces (approximately 30% of dose) with minimal excretion in the urine (approximately 0.1%).

In a more extensive time-course pharmacodynamic study, twelve animals were dosed (20 mg/kg WR-171,669-¹⁴C) and two animals were sacrificed at time intervals of 2, 4, 6, 8, 24 and 48 hr. Total radioactivity peaked for both whole blood and plasma samples at 4 hr with a secondary peak in radioactivity for both at 8 hr. Plasma radioactivity concentrations were higher than blood at all times. The plasma half-life for total radioactivity was estimated to be 46 hr with a rate constant of 0.015 hours⁻¹ (Report I, June 4, 1973). Urinary excretion was minimal with only 0.16% of the dose excreted in 48 hr. The majority of the radioactive dose was present in the feces, with 39.8% at 24 hr and 64.6% at 48 hr. No radioactivity was expired as CO₂ (Report II, June 6, 1973).

Absorption of the compound was slow (at 2 hr, 84.35% of dose vs. at 8 hr, 17.16% of dose in the GI tract). This was also supported by the fact that at 8 hr 10.30% of the dose was excreted in the feces. It is therefore likely that total absorption was never attained. Tissue levels maximized between 4 and 6 hr with spleen, liver, kidney, lung, adrenal glands and fat reaching the highest levels. Most tissues also demonstrated a rebound of radioactivity concentration at 24 hr, which probably suggests the enterohepatic circulation of the compound. The total activity in the carcass peaked at 8 hr (51.16% of dose) and was approximately half that value at 48 hr (24.76% of dose) (Report III, June 8, 1973).

Chromatographic separation of the methanol extract of feces with thin layer chromatography demonstrated two radioactive peaks or fractions. The principal fraction (designated I) had an R_F of 0.55-0.60, was co-chromatographic with authentic WR-171,669-¹⁴C, and quantitatively accounted for 72.7 to 89.6% of the radioactivity analyzed by thin layer chromatography. A secondary radioactive fraction, and presumably a metabolic product of the parent compound, was present at an R_F of 0.35 to 0.39 and accounted for 10.4 to 27.3% of the activity analyzed (Report IV, June 26, 1973).

ABSORPTION, DISTRIBUTION AND EXCRETION OF WR-159,412-¹⁴C IN THE RAT

Radiochemically pure WR-159,412-¹⁴C was orally administered in a single dose (40 mg/kg) to sixteen male Sprague-Dawley rats, and two animals were sacrificed at time intervals of 1, 2, 3, 4, 5, 6, 24 and 48 hr. Radioactivity levels in blood, plasma and red blood cells showed significant radioactivity at 1 hr. Blood and red blood cell levels of radioactivity were always higher than plasma levels. However, there was also significant rebound of the radioactive concentration in these fractions at 3 hr and 6 hr. These data would suggest the occurrence of enterohepatic circulation of the compound (Report V, July 2, 1973).

The primary route of excretion was via the feces with 2.03%, 59.41% and 66.49% being excreted at 6 hr, 24 hr and 48 hr, respectively. The urinary levels at 6 hr, 24 hr and 48 hr were 1.04%, 1.82% and 2.33%, respectively. Thus, major excretion occurred within the first 24 hr. Expired CO₂ did not have any radioactivity (Report VI, July 3, 1973).

Tissue distribution of the compound was greatest in the lungs, liver and kidneys. The levels of radioactivity both in these tissues and in the carcass appeared to remain fairly constant throughout the first 24 hr. A significant decline was noted in all tissues and carcasses by 48 hr. It is important to note, however, that at all time intervals, approximately 85% or greater of the radioactivity was accounted for in the gastrointestinal tract, carcass or feces. Furthermore, the vast majority was either in the feces or gastrointestinal tract; although the radioactivity did appear in the blood, tissues and carcass, it is likely that absorption of the drug was only partial (Report VII, July 9, 1973).

The principal product extracted from the feces with methanol was found to be co-chromatographic with the parent compound (R_F 0.13-.22). This radiolabeled fraction accounted for 76.5 to 88.7% of the radioactivity analyzed by thin layer chromatography. The remainder of the radioactivity in each analysis was found at the chromatographic origin (Report VIII, July 20, 1973).

ABSORPTION, DISTRIBUTION AND EXCRETION OF WR-159,412-¹⁴C IN THE RHESUS MONKEY

Radiochemically pure WR-159,412-¹⁴C was given in a single oral dose (5 mg/kg) to four male rhesus monkeys. At one hour, there was radioactivity present in the whole blood, the plasma and the red blood cells. The time interval for maximum concentration in the three fractions was exceedingly variable and collectively suggested that there was both a lengthy absorption and an enterohepatic circulation of the compound. The plasma levels were consistently higher than red blood cell levels at each time period. When plasma and red blood cell levels were averaged and plotted, the radioactivity in the plasma had a half-life of 54 hr, an elimination rate constant of 0.0128 hr^{-1} , and an absorption rate constant of 0.173 hr^{-1} . The radioactivity in the red blood cells gave values of 59 hr, 0.0117 hr^{-1} and 0.462 hr^{-1} , respectively (Report IX, July 24, 1973).

Significant amounts of the radioactivity appeared in the urine after dosing at 24 hr (9.77%) and 48 hr (8.45%). Another 7.2% accumulated more slowly out to 192 hr. Total urinary excretion was 28.72%. Radioactivity was present in the feces at 24 hr (1.21%) with maximum excretion at 96 hr (15.49%) and 120 hr (15.83%). Total fecal excretion was 50.14% at 192 hr. Lengthy fecal excretion patterns would support the blood pharmacokinetic findings of prolonged circulation (Report X, August 8, 1973).

The liver (8.06% of the dose), cerebrum (0.95%), lung (2.21%), eye (0.68%) and kidney (0.65%) had the highest accumulation of radioactivity at 24 hr. Interestingly, the eye radioactivity content in the 48 hr animal had an even greater value of 1.38% of the dose. The radioactivity content of the gastrointestinal tract was high at 24 hr (28.66% of the dose), 48 hr (35.02%) and 72 hr (42.25%) and these findings would also support the lengthy absorption, circulatory presence and enterohepatic circulation of the compound. Concomitantly, the percent of dose in the bile over those intervals also increased (0.4%-24 hr, 2.3%-48 hr, 6.2%-72 hr) and thus would confirm the concept of enterohepatic circulation (Report XI, August 9, 1973).

In order to better understand the concentrating phenomenon of WR-159,412-¹⁴C in the eye, a lengthy pharmacodynamic study was performed. Following the oral dosing, animals sacrificed at 1 week, 2 weeks, 1 month and 6 months demonstrated a concentration of carbon-¹⁴ radioactivity in the eyes even at 6 months (0.03% of the dose). The only other organ with measurable radioactivity was the lung (0.01%) at the 6-month time interval (Reports XVII and XVIII, February 12, 1974).

ABSORPTION, DISTRIBUTION, AND EXCRETION OF WR-171,669-¹⁴C IN THE RHESUS MONKEY

Radiochemically pure WR-171,669-¹⁴C was given orally (5 mg/kg) in a single dose to five male rhesus monkeys. Radioactivity was present in the whole blood, the plasma and the red blood cells at 1 hr following presentation of the dose. The plasma levels were consistently higher than whole blood levels at each time period. There was considerable individual variation with respect to peak levels of radioactive concentration in the blood compartments. The plasma level of radioactivity peaked in 4 of the 5 monkeys between 4 and 6 hr. Following this peak of radioactivity, there was a lengthy or prolonged circulation of the compound to at least 192 hr (Report XIII, October 25, 1973).

Excretion was primarily in the feces with 2.87% of the dose appearing in the first 24 hr and 74.60% accumulating to 192 hr. Urinary excretion was insignificant with 0.21% of the dose accumulated at 24 hr and 1.45% at 192 hr (Report XIV, October 28, 1973). The highest concentration of tissue radioactivity at 24, 48 and 72 hr was in the liver and lung. The total radioactivity of excised organs was 2.52% of the dose at 24 hr and 6.70% at 72 hr. Interestingly, 71.69% of the dose was still in the stomach at 24 hr, but this did decline to 0.17% at 72 hr. This finding was in basic agreement with the prolonged fecal excretion, the lengthy partial absorption and the circulation of the compound (Report XV, November 1, 1973).

Thin layer chromatographic separation of the methanol extract of the fecal radioactivity revealed the presence of two radiolabeled fractions. Fraction I had an R_F of 0.55 to 0.63, was chromatographically similar to authentic WR-171,669-¹⁴C (R_F 0.60) and accounted for 92-100% of the radioactivity analyzed. The second fraction, designated II when present, had an R_F of 0.34 to 0.42 and accounted for 2 to 8% of the radioactivity analyzed. It was presumed to be a metabolite of the parent compound (Report XVI, November 15, 1973).

ABSORPTION, DISTRIBUTION, EXCRETION AND BIOTRANSFORMATION OF WR-172,
435-¹⁴C IN THE RAT

Radiochemically pure WR-172,435-¹⁴C was given orally in a single dose (10 mg/kg) to each of 16 male rats. Two animals were terminated at each of the time intervals of 1, 2, 4, 5, 6, 24, 48 and 72 hr. The ¹⁴C radioactivity was present in the circulation at 1 hr, and the radioactive concentration peaked at 2 hr for blood, plasma and red blood cells. The concentration in these compartments rebounded at 5 hr, which would suggest the occurrence of enterohepatic circulation. Plasma radioactivity levels were greater than or equal to blood radioactivity levels at each time period. The plasma radioactivity had a half-life of 11.5 hr and a rate constant of 0.06 hr⁻¹. The red blood cell pharmacokinetic values were 16 hr and 0.04 hr⁻¹, respectively (Report 19, May 14, 1974).

Small amounts of radioactivity appeared in the feces at 1 hr (0.09% of dose), and 89.53% had accumulated at 72 hr. The urine contained 0.02% at 1 hr and only 0.08% at 72 hr. No radiolabeled CO₂ was measured in these experiments (Report 20, May 14, 1974). Highest tissue concentrations were attained at 5 hr with liver (7.70% of dose), lungs (1.22%) and kidneys (0.56%) having the greatest. These low tissue levels were in agreement with the fact that 66.77% of the dose was still present in the gastrointestinal tract at 5 hr. The carcass contained 20.21% of the dose at this time interval. These excretory and pharmacodynamic data would suggest a slow, partial absorption of the compound (Report XXI, October 2, 1974).

Three radioactive fractions were obtained from thin layer chromatographic analysis of the fecal methanol extract. The predominant fraction (III) had an R_F of 0.61 to 0.65, was chromatographically similar to the parent compound, and accounted for 46 to 85% of the radioactivity analyzed. Radiolabeled fraction II had an R_F of 0.42 to 0.44 and accounted for 3 to 7% of the radioactivity analyzed. Fraction I had an R_F of 0.16 to 0.24 and contained 13 to 46% of the radioactivity analyzed (Report 22, May 28, 1974).

ABSORPTION, DISTRIBUTION, EXCRETION AND BIOTRANSFORMATION OF WR-184,
806-¹⁴C IN THE RAT (ORAL DOSE)

Radiochemically pure WR-184,806-¹⁴C was presented in a single oral dose (10 mg/kg) to each of sixteen male rats. Two animals were sacrificed at each of the time intervals of 0.5, 1, 2, 3, 4, 8, 24 and 48 hr. Radioactivity had appeared in the blood at 0.5 hr, and the radioactive concentration peaked in plasma and whole blood at 1 hr. Plasma radioactivity was consistently higher than the whole blood at all times except at 24 and 48 hr where the reverse was true. The estimated plasma half-life and disappearance constant were 2 hr and 0.346 hr⁻¹, respectively (Report XXIII, August 30, 1974).

Excretion was primarily in the feces with 0.01%, 65.16% and 82.84% of the radiolabeled dose cleared at 0.5 hr, 24 hr and 48 hr, respectively. Urinary excretion was minimal, with less than 0.1% at 0.5 hr and 2.28% of the presented dose accumulated at 48 hr (Report XXIV, August 30, 1974). Absorption of this compound appeared to be rapid since at 0.5 hr the liver (12.97%), lungs (0.76%), kidneys (0.28%) and heart (0.08%) contained a notable percentage of the dose. All excised organs and the carcass, exclusive of the contents of the gastrointestinal tract, contained 45.60% of the dose at 0.5 hr, which suggests significant absorption and very broad distribution of the compound. This value had declined to 11.27% of the dose at 8 hr, 5.46% at 24 hr and 1.71% at 48 hr (Report XXV, August 30, 1974).

The fecal excretory products contained principally the parent compound as indicated by thin layer chromatography (R_f -0.39 to 0.55). One purification, however, suggested the presence of a principal metabolic product having an R_f of 0.18. The situation was also complicated by the fact that chromatographic analysis of the contents of the small intestine gave multiple radiolabeled fractions. Resolution of these products requires further study (Report XXVI, August 30, 1974).

ABSORPTION, DISTRIBUTION, EXCRETION AND BIOTRANSFORMATION OF WR-184,
806-¹⁴C IN THE RHESUS MONKEY

Radiochemically pure WR-184,806-¹⁴C was given in a single oral dose (10 mg/kg) to each of seven male rhesus monkeys. Significant radioactivity was present in the blood at 2 hr after dosing. The radioactivity in the blood and plasma peaked simultaneously, and in all instances there was a greater radioactivity concentration in the plasma. The time interval at which the radioactivity peaked was individually variable and demonstrated both slow absorption and prolonged circulation. The plasma radioactivity half-life was 52 hr and the rate constant 0.013 hr⁻¹ (Report XXVII, September 25, 1974).

Significant amounts of the compound were excreted in the urine at 24 hr (22.42% of the dose) and 62.73% accumulated by 312 hr. However, 57.80% of the dose had already appeared at 96 hr. Fecal excretion was also significant with 1.28% at 24 hr and 20.49% at 120 hr. Ultimately, 25.55% of the dose accumulated at 312 hr. This rather lengthy excretion agrees with the prolonged blood circulation (Report XXVIII, September 25, 1974). Absorption of the compound was supported by the fact that 17.18% of the dose was present in excised organs at 24 hr with lungs (2.42%), liver (7.03%), muscle (7.08%) and cerebellum (1.13%) being the principal tissues of radioactive concentration. Interestingly, 30.33% of the dose was still present in the stomach contents at 8 hr but declined to 0.16% at 24 hr. Bile also had significant amounts of radioactivity with 0.72% at 8 hr and 5.54% at 48 hr. This significant amount of radioactivity in the bile at 48 hr would attest to significant entero-hepatic circulation (Report XXIX, September 27, 1974).

ABSORPTION, DISTRIBUTION, EXCRETION AND BIOTRANSFORMATION OF WR-33063-¹⁴C
IN THE RHESUS MONKEY

Radiochemically pure WR-33063-¹⁴C was given as a single oral dose (30 mg/kg) to six male rhesus monkeys. Radioactivity was present in the circulation of five of six monkeys at 1 hr and in all animals at 2 hr. The time interval for maximum radioactive accumulation was variable; however, for all animals during the first 24 hr of the study, the mean maximum level in blood and plasma was at 4 hr. Significant rebounds of the blood radioactivity were frequently seen and would support the presence of enterohepatic circulation. The estimated plasma half-life for total radioactivity was 7 hr and the rate constant was 0.099 hr⁻¹. The plasma radioactivity levels were constantly higher than whole blood levels at all time periods (Report XXXI, February 15, 1975).

Only 0.74% of the dose had appeared in the urine at 24 hr, and 2.70% ultimately accumulated at 360 hr. In contrast, 6.86% of the dose was excreted in the feces by 24 hr and 71.01% was present by 96 hr. The final accumulation in the feces was 74.85% at 360 hr (Report XXXII, February 15, 1975). Very small amounts of radioactivity were present in the tissues. The musculature had 0.20%, 0.23%, and 0.26% of the dose at 24, 48, and 72 hr, respectively. The liver had 0.21%, 0.16% and 0.10% at these time intervals, respectively.

Significant amounts of the dose were present in the gastrointestinal tract at 24 hr (87.78%), 48 hr (61.33%) and 72 hr (6.69%). The radioactivity content in bile was low (0.21% at 24 hr, 1.23% at 48 hr, and 0.29% at 72 hr). These excretory and pharmacodynamic data imply that the compound was poorly absorbed and had a low tissue distribution (Report XXXIII, February 15, 1975).

ABSORPTION, DISTRIBUTION, EXCRETION AND BIOTRANSFORMATION OF WR-184,
806-¹⁴C IN THE RAT (INTRAVENOUS DOSE)

Radiochemically pure WR-184,806-¹⁴C was given intravenously in a single dose (10 mg/kg) via the tail vein to 18 male rats. Two rats were sacrificed at each of the time intervals of 0, 0.1, 0.25, 0.33, 0.5, 1.0, 4, 24 and 48 hr after dosing. Radioactivity was circulating in the blood immediately after dosing as would be expected. Radiochemical analysis demonstrated an exponential decline of the radioactivity and a half-life of 12 hr and a rate constant of 0.058 hr⁻¹ were calculated. There was evidence in the early circulation data (1-4 hr) that the absorption rate was variable. Furthermore, plasma and blood radioactivity levels were variable with respect to which of the components was greater (Report XXXIV, May 15, 1975).

The main excretion of the carbon-¹⁴ radioactivity was through the feces. A measurable amount was present in both excretory compartments at 4 hr. Urine had 0.42% of the dose and feces had 1.09%. At 48 hr, the urine had accumulated 4.09% of the dose, whereas the feces had accumulated 53.85% (Report XXXV, May 15, 1975). The uptake of the compound by the body organs was minimal. The maximum percent of the dose in the liver was 2.03% (4 hr); in the lungs, 3.01% (15 min); and in the kidneys, 0.63% (30 min). Conversely, a large percentage was in the carcass at 10 min (approx. 97.8% of the dose) and this percentage had rapidly declined by 4 hr (approx. 47.6%). At 24 hr, the carcass values were approximately 11.1% of the radioactive dose. Thus, in consideration of the very low body organ concentration, it is presumed that the radioactivity had accumulated primarily in muscle, bone, fat and other peripheral tissues (Report XXXVI, May 15, 1975).

LIST OF INTERIM REPORTS

- REPORT NO. I - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rat (January 26, 1973 and June 4, 1973)
- REPORT NO. II - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rat (June 6, 1973)
- REPORT NO. III - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rat (June 8, 1973)
- REPORT NO. IV - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rat (June 26, 1973)
- REPORT NO. V - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rat (July 2, 1973)
- REPORT NO. VI - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rat (July 3, 1973)
- REPORT NO. VII - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rat (July 9, 1973)
- REPORT NO. VIII - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rat (July 20, 1973)
- REPORT NO. IX - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rhesus Monkey (July 24, 1973)
- REPORT NO. X - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rhesus Monkey (August 8, 1973)
- REPORT NO. XI - Absorption, Distribution and Excretion of WR-159, 412-C¹⁴ in the Rhesus Monkey (August 9, 1973)
- REPORT NO. XIII - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rhesus Monkey - "Blood and Plasma Levels of WR-171, 669-C¹⁴" (October 27, 1973)
- REPORT NO. XIV - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rhesus Monkey (October 28, 1973)
- REPORT NO. XV - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rhesus Monkey - "Tissue Distribution of WR-171, 669-C¹⁴" (November 1, 1973)
- REPORT NO. XVI - Absorption, Distribution and Excretion of WR-171, 669-C¹⁴ in the Rhesus Monkey - "Metabolic Profile of WR-171, 669-C¹⁴" (November 15, 1973)

LIST OF INTERIM REPORTS (Continued)

- REPORT NO. XVII - Absorption, Distribution and Excretion of WR-159, 412-¹⁴C in the Rhesus Monkey "Blood and Plasma Levels of WR-159, 412-C¹⁴" (February 12, 1974)
- REPORT NO. XVIII - Absorption, Distribution and Excretion of WR-159, 412-¹⁴C in the Rhesus Monkey "Tissue Distribution of WR-159, 412-C¹⁴" (February 12, 1974)
- REPORT NO. 19 - Absorption, Distribution, Excretion and Biotransformation of WR-172, 435-C¹⁴ in the Rat - "Blood and Plasma Levels of WR-172, 435-C¹⁴" (May 14, 1974)
- REPORT NO. 20 - Absorption, Distribution, Excretion and Biotransformation of WR-172, 435-C¹⁴ in the Rat - "Excretion of WR-172, 435-C¹⁴" (May 14, 1974)
- REPORT NO. XXI - Absorption, Distribution, Excretion and Biotransformation of WR-172, 435-C¹⁴ in the Rat - "Tissue Distribution of WR-172, 435-C¹⁴" (October 2, 1974)
- REPORT NO. 22 - Absorption, Distribution, Excretion and Biotransformation of WR-172, 435-C¹⁴ in the Rat - "Biotransformation of WR-172, 435-C¹⁴" (May 28, 1974)
- REPORT NO. XXIII - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rat - "Blood and Plasma Levels of WR-184, 806-C¹⁴" (August 30, 1974)
- REPORT NO. XXIV - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rat - "Excretion of WR-184, 806-C¹⁴" (August 30, 1974)
- REPORT NO. XXV - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rat - "Tissue Distribution of WR-184, 806-C¹⁴" (August 30, 1974)
- REPORT NO. XXVI - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rat - "Biotransformation of WR-184, 806-C¹⁴" (August 30, 1974)
- REPORT NO. XXVII - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rhesus Monkey - "Blood and Plasma Levels of WR-184, 806-C¹⁴" (September 25, 1974)
- REPORT NO. XXVIII - Absorption, Distribution, Excretion and Biotransformation of WR-184, 806-C¹⁴ in the Rhesus Monkey - "Urinary and Fecal Excretion of WR-184, 806-C¹⁴" (September 25, 1974)

LIST OF INTERIM REPORTS (Continued)

- REPORT NO. XXIX - Absorption, Distribution, Excretion and Biotransformation of WR-184,806-C¹⁴ in the Rhesus Monkey - "Tissue Distribution of WR-184,806-C¹⁴" (September 27, 1974)
- REPORT NO. XXXI - Absorption, Distribution, Excretion and Biotransformation of WR-33063-C¹⁴ in the Rhesus Monkey - "Blood and Plasma Levels of WR-33063-C¹⁴" (February 15, 1975)
- REPORT NO. XXXII - Absorption, Distribution, Excretion and Biotransformation of WR-33063-C¹⁴ in the Rhesus Monkey - "Urinary and Fecal Excretion of WR-33063-C¹⁴" (February 15, 1975)
- REPORT NO. XXXIII - Absorption, Distribution, Excretion and Biotransformation of WR-33063-C¹⁴ in the Rhesus Monkey - "Tissue Distribution of WR-33063-C¹⁴" (February 15, 1975)
- REPORT NO. XXXIV - Absorption, Distribution, Excretion and Biotransformation of WR-184,806-C¹⁴ in the Rat - "Blood and Plasma Levels of WR-184,806-C¹⁴ After Intravenous Administration" (May 15, 1975)
- REPORT NO. XXXV - Absorption, Distribution, Excretion and Biotransformation of WR-184,806-C¹⁴ in the Rat - "Excretion of WR-184, 806-C¹⁴ after Intravenous Administration" (May 15, 1975)
- REPORT NO. XXXVI - Absorption, Distribution, Excretion and Biotransformation of WR-184,806-C¹⁴ in the Rat - "Tissue Distribution of WR-184,806-C¹⁴ after Intravenous Administration" (May 15, 1975)

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